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Diurnal variation in left ventricular function: a study of patients with myocardial ischaemia, syndrome X, and of normal controls

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SUMMARY Angina can occur in the early morning. The mechanism of this is unclear and both haemodynamic changes and coronary artery spasm may be important. The purpose of this study was to investigate the diurnal variation in pulmonary artery diastolic pressure (an indirect measure of left ventricular filling pressure) in six normal subjects, 18 patients with coronary artery disease, five with variant angina, and six with syndrome X. A transducer tipped catheter and a simple recording system were used to record ambulatory pulmonary artery diastolic pressure for 24 hours. Variation in pulmonary artery diastolic pressure was related to the timing of episodes of ST segment depression and elevation by simultaneously recording a frequency modulated electrocardiogram. Episodes of ST segment change occurred predominantly in the early morning (midnight to 6 am) in variant angina (eight out of 14 episodes) whereas in syndrome X all episodes were recorded during the day. In coronary artery disease both painful and painless episodes were distributed throughout the day, with 10 out of 67 episodes occurring between midnight and 6 am. A similar diurnal variation in pulmonary artery diastolic pressure was seen in the groups—that is, values were low during the day and higher at night, with the maximum values between midnight and 6 am. The 24 hour median pulmonary artery diastolic pressure was higher in patients with coronary artery disease than in the control group and those with syndrome X.

The finding that pulmonary artery diastolic pressure, and therefore left ventricular end diastolic pressure, is greatest in the early morning may represent the background haemodynamic state in which other factors lead to myocardial ischaemia during these hours.

There is a well described diurnal variation in several physiological variables such as blood pressure, heart rate, cortisol, and catecholamines.[1–4] This may have adverse consequences; for example myocardial infarction and cerebral infarction both show diurnal variation.[5,6] Angina may occur not only when the patient is active through the day but also in the early hours of the morning.[7–9] Various pathophysiological mechanisms have been proposed, including an increase in myocardial oxygen consumption in patients with severe coronary artery disease and coronary spasm in patients with variant angina.[10,11] Angina decubitus, first described by Heberden, is probably caused by increased left ventricular filling pressure secondary to increased venous return when the patient lies down in bed.[12] It has not been possible previously to investigate the importance of left ventricular filling pressure as a mechanism of myocardial ischaemia.

We have developed a technique for recording ambulatory pulmonary artery diastolic pressure.[13] This provides a means of assessing left ventricular filling pressure in normal subjects and patients with ischaemic heart disease during unrestricted activity. The purpose of this study was to determine whether there is diurnal variation in left ventricular filling pressure, because this may have an important bearing on the pathophysiological mechanisms of nocturnal angina.

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Patients and methods

We studied 29 patients (28 men, 1 woman). All were shown on the basis of clinical history and coronary angiography to have various coronary ischaemic syndromes. Eighteen patients had atherosclerotic coronary artery disease (mean (SD) age 57 (11) years), five patients had variant angina (mean age 51 (8) years) and six patients had syndrome X (mean age 48 (12) years).

Normal controls—Six control subjects (5 men, 1 woman) were studied (mean age 39 (6·6) years). These subjects presented with atypical chest pain; they had negative exercise tests and normal coronary arteries at angiography. The results of 24 hour ambulatory ST segment monitoring was entirely normal.

Coronary artery disease—All had angiographic evidence of coronary artery disease: 14 had three vessel disease, three had two vessel disease, and one had single vessel disease.

Variant angina—These patients had clinical, and angiographic or electrocardiographic evidence or both of coronary artery spasm: one had normal coronary arteries and four had coronary artery disease.

Syndrome X—These were patients who gave a history of chest pain but were shown to have normal coronary arteries despite a positive exercise test with at least 1 mm ST segment depression recorded on exercise.

All antianginal medication other than glyceryl trinitrate was discontinued at least 48 hours before the study. The pulmonary artery pressure was monitored for at least 24 hours and where possible for up to 48 hours. The frequency modulated ST segment was monitored throughout this period.

The study was approved by the ethics committee and the patients gave their informed consent.

The transducer tipped pulmonary artery catheter was introduced percutaneously via the subclavian vein to a proximal pulmonary artery under fluoroscopic control in the cardiac catheter laboratory when the patient had cardiac catheterisation. A polyurethane six French NIH type catheter with a miniature strain gauge transducer mounted on the tip was used. The transducer was driven and demodulated by an electrically isolated Gaeltec amplifier. Pulmonary artery pressure was recorded on an Oxford Medilog 1 miniature tape recorder that had been modified by the insertion of an AM4 pressure module.

The ST segment was monitored on a frequency modulated recorder and leads CM2 and CM5 were recorded. The electrocardiogram was replayed on an Oxford MA20 scanner. Changes in the ST segment were measured 80 ms after the J point. A change of 1 mm ST segment depression was considered significant. The heart rate and ST segment changes were analysed on a beat to beat basis for five minutes before each episode and again for five minutes after the ST segment had returned to basal levels.

Patients were then asked to perform normal daily activities and were fully ambulant during the 24 hours of recording. Patients kept diaries during the period that ambulatory pulmonary artery pressure and the ST segment were monitored. The pulmonary artery pressure trace was replayed via a PB2 unit and a PM3 amplifier. Recordings of the pulmonary artery diastolic pressure were displayed on ultraviolet paper and measured with a calibrated scale from a zero reference point. The pulmonary artery diastolic pressure was measured every fifteen minutes throughout the 24 hour period for each patient. For the purposes of analysis and display, values were normalised by expressing them as a ratio of the 24 hour mean pulmonary artery diastolic pressure for that patient.

Wilcoxon rank sum testing was performed on both the ratios and the absolute values.

Results

The table shows the 24 hour changes in pulmonary artery diastolic pressure for each group of patients. In each individual patient the mean pulmonary artery diastolic pressure over 24 hours was calculated and analysis was performed both on ratios and on absolute values. The statistical results were the same by both methods of calculation. For the purpose of clarity only the ratios are presented.

Normal controls—Figure 1 shows the diurnal variation in pulmonary artery diastolic pressure. Pulmonary artery diastolic pressure was significantly higher between midnight and 6 am than during the remainder of the 24 hours ($p < 0·01$).

Coronary artery disease—Figure 2 shows the diurnal variation in pulmonary artery diastolic pressure in the 18 patients with coronary artery disease. Again

Table *Twenty four hour median (range) pulmonary artery diastolic pressure for normal controls, patients with coronary artery disease, coronary artery spasm, and syndrome X*

	Number of patients	*24 hour pulmonary artery diastolic pressure (mm Hg)*
Normal controls	6	4·3 (2·1–7·6)
Coronary artery disease	18	8·1 (2·5–12·6)*
Variant angina	5	4·7 (3·3–16·3)
Syndrome X	6	2·9 (1·5–5·7)†

*Patients with coronary artery disease had a greater median pulmonary artery diastolic pressure than the controls ($p < 0·05$).
†Pulmonary artery diastolic pressure was lower in patients with syndrome X than in those with coronary artery disease ($p < 0·01$) but similar to that in controls.

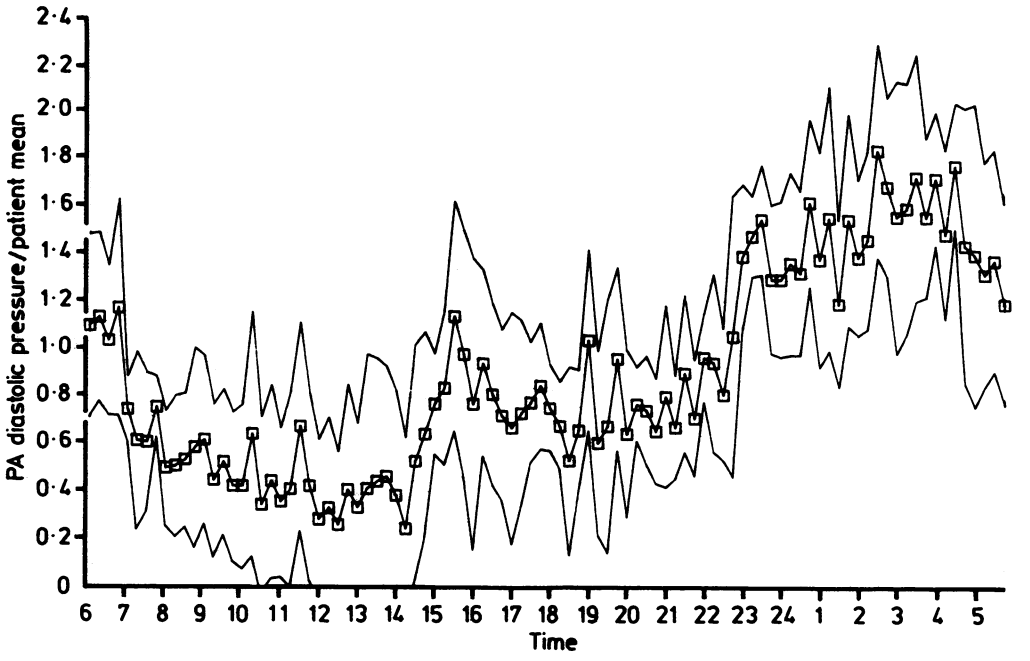

Fig 1 *Diurnal variation of pulmonary artery (PA) diastolic pressure in six normal subjects. Pulmonary artery diastolic pressure was significantly higher at night ($p < 0{\cdot}01$). Pulmonary artery diastolic pressure was measured throughout the 24 hour period for each patient and the values were normalised by expressing them as a ratio of the 24 hour mean pulmonary artery diastolic pressure for each patient. Mean pulmonary artery diastolic pressure (SD) is shown.*

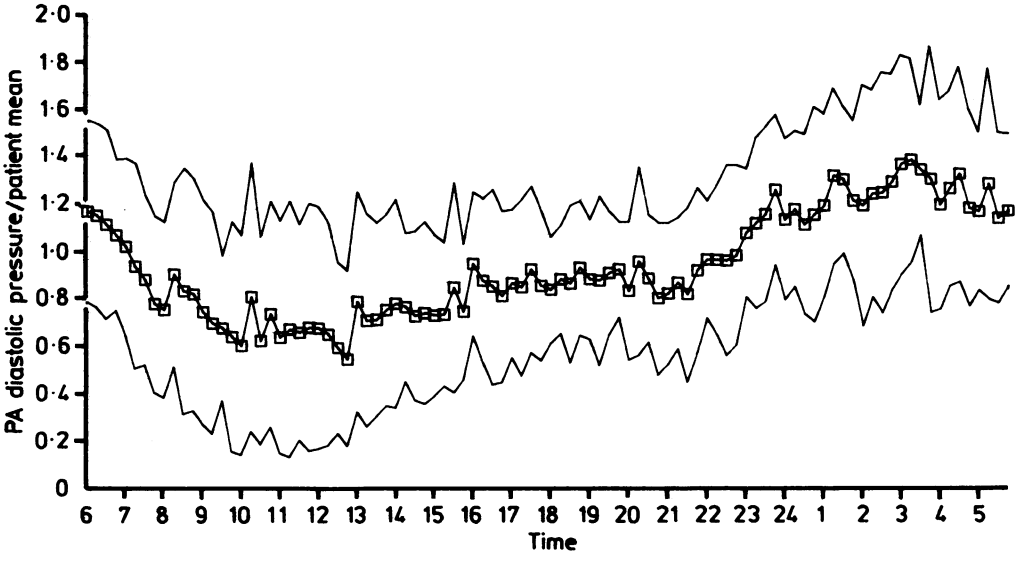

Fig 2 *Diurnal variation of pulmonary artery diastolic pressure in 18 patients with coronary artery disease. Pulmonary artery diastolic pressure was significantly higher at night ($p < 0{\cdot}01$). See legend to fig 1.*

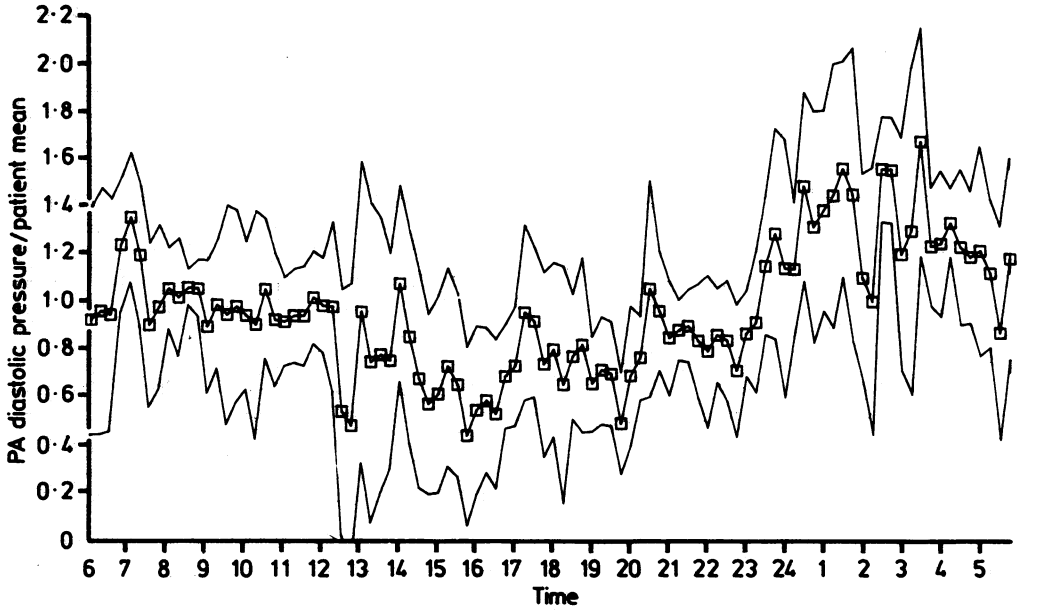

Fig 3 *Diurnal variation of pulmonary artery diastolic pressure in five patients with coronary artery spasm. Pulmonary artery diastolic pressure was significantly higher at night ($p < 0{\cdot}01$). See legend to fig 1.*

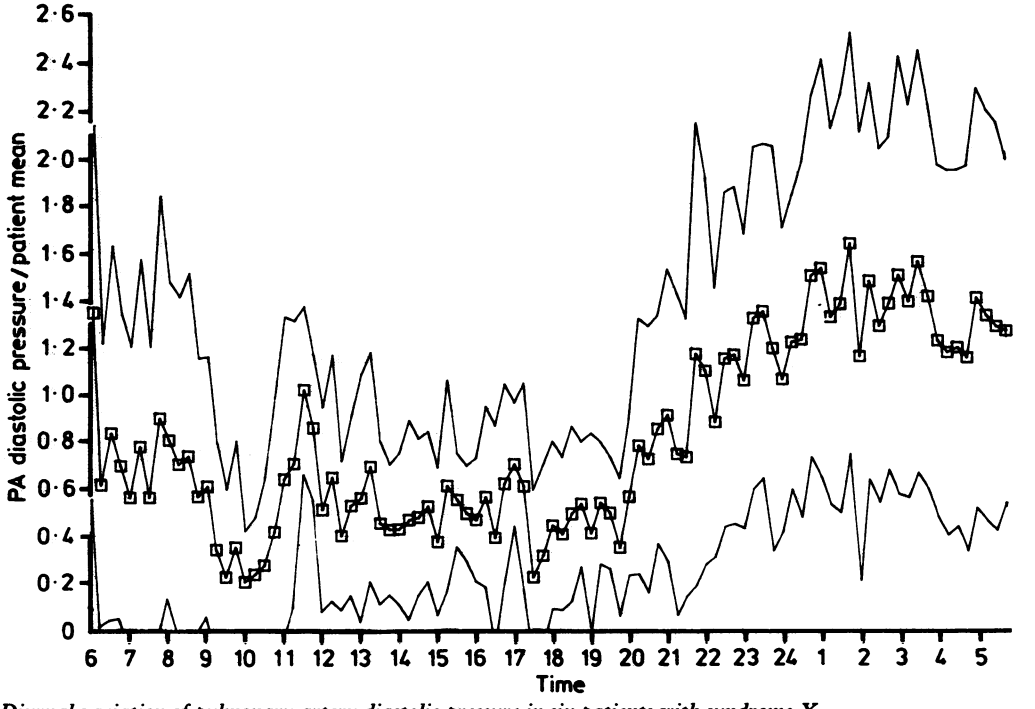

Fig 4 *Diurnal variation of pulmonary artery diastolic pressure in six patients with syndrome X. Pulmonary artery diastolic pressure was significantly higher at night ($p < 0{\cdot}01$). See legend to fig 1.*

there was a significant rise in the pulmonary artery diastolic pressure between midnight and 6 am ($p < 0.01$). Ten of the total of 67 episodes of ST segment depression occurred during this six hour period. The 24 hour median pulmonary artery diastolic pressure in patients wth coronary artery disease (8·1 mm Hg, range 2·5–12·6) was greater than that in the control group (median 4·3 mm Hg, range 2·1–7·6) ($p < 0.05$).

Variant angina—Figure 3 shows the diurnal variation of pulmonary artery diastolic pressure in the five patients with variant angina. There was a significant rise in pulmonary artery diastolic pressure between the hours of midnight and 6 am ($p < 0.01$). In this group there were eight episodes of ST segment elevation between midnight and 6 am and six episodes at other times.

Syndrome X—Figure 4 shows the diurnal variation in pulmonary artery diastolic pressure in patients with syndrome X. There was a significant rise in pulmonary artery diastolic pressure between the hours of midnight and 6 am ($p < 0.01$). All episodes of ST segment depression occurred during the day when the patients were exercising. The 24 hour median pulmonary artery diastolic pressure was lower in patients with syndrome X (2·9 mm Hg, range 1·5–2·7) than those with coronary artery disease (median 8·1 mm Hg, range 2·5–12·6) ($p < 0.01$) but did not differ from that in the control group.

Discussion

Various mechanisms have been proposed to explain the precipitation of angina pectoris in patients with coronary artery disease. Angina pectoris is usually regarded as being the result of an increase in myocardial oxygen demand; however, recently alterations in coronary tone have been emphasised.[10 14]

At night patients with severe coronary disease often have an increase in heart rate before the onset of ST segment depression and the development of angina, possibly due to alterations in the phase of sleep associated with turning in bed, rapid eye movement sleep, and dreaming.[10 15–17] This increase in heart rate is, however, often less than that required to precipitate angina during the day. In such circumstances it has been suggested that an increase in coronary artery tone, possibly due to increased vagal activity, is also important.[14] Platelet aggregation will cause the release of thromboxane A_2, which is a potent vasoconstrictor; studies have shown a reduction in nocturnal myocardial ischaemia when platelet inhibitors are given.[18]

It has long been known that dilatation of the left ventricle[19] and increase in left ventricular filling pressure[20] are early events after myocardial ischaemia and will increase myocardial oxygen demand. To some extent this has been ignored as a mechanism of angina pectoris because of the difficulties of investigating this phenomenon. In previous studies of the haemodynamic changes in patients with angina fluid filled catheters have been used and the studies have been performed either in the catheter laboratory or coronary care unit.[20 21] The use of a transducer tipped catheter has avoided the problems of a fluid filled system, such as a low resonant frequency and the need for a transducer-perfusion unit with a constant zero reference point.[13 22 23]

In this study we have been able to measure the left ventricular filling pressure indirectly by measuring pulmonary artery diastolic pressure in ambulant subjects. Patients with coronary artery disease had a higher 24 hour median pulmonary artery diastolic pressure than the control group and patients with syndrome X.

For the first time a diurnal variation in the left ventricular filling pressure has been demonstrated. At night there were significant increases in left ventricular filling pressure in all groups of patients. The rise was less in patients with coronary artery disease than in the other groups though this difference is not significant. When a person lies down both pulmonary blood flow and pulmonary blood volume increase because of increased venous return.[24 25] It is therefore not surprising that we saw a diurnal rhythm in left ventricular filling pressure; however, the nocturnal rise occurred several hours after lying down. The rise in pulmonary artery diastolic pressure is unlikely to be due to myocardial ischaemia because it was seen in all groups. Episodes of nocturnal ischaemia are short lived whereas the rise in left ventricular filling pressure occurs gradually and lasts the whole night. The nocturnal rise in left ventricular filling pressure may be important in providing the setting for alterations in coronary tone or myocardial oxygen demand in patients with and without coronary artery spasm. It may also have important therapeutic implications because drugs that reduce left ventricular filling pressure such as nitrates may be particularly beneficial.

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